

REMARKS

Following entry of the amendment as requested herein, Claims 1, 14, 16-18, 20, 24-40, 42, 43, and 46-55 are pending in the present application. Claims 53-55 are new claims added herein. Claims 2-13, 15, 19, 21-23, 41, and 44-45 are cancelled without prejudice.

Independent Claim 1 is amended without prejudice to focus the present application on an embodiment of the invention wherein it is a method of treating a condition associated with CSD in a subject. This amendment is requested in the interest of advancing prosecution by reducing the number of issues in examination. No admission is made that the claim as previously presented is not patentable.

Claim 1 is also amended and recites a method wherein the condition associated with CSD is a chronic headache selected from a group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, and an inflammatory headache. Support for Claim 1 is found in the specification as filed at p. 11, lines 11-19.

Claim 27 is amended and recites a method wherein the compound is administered at a dose of at a maximum 1 g/day. Support for Claim 27 is found in the specification as filed at p. 26, lines 23-26.

Claim 33 is amended for clarity to recite a CSD condition. Support for Claim 33 is found in the specification as filed at p. 27, lines 26-31.

Claim 46 is amended and recites a method of suppressing CSD to prevent or treat a headache selected from the group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, and an inflammatory headache. Support for Claim 46 is found in the specification as filed at p. 10, line 32 and 11, lines 1 and 11-24.

New Claim 53 recites a method wherein the further active agent is effective for treatment of a CSD-associated condition selected from the group consisting of head injury, transient global amnesia, and intracranial hemorrhage. Support for Claim 53 is found in the specification as filed at p. 10, lines 11-12 and 24.

New Claim 54 recites a method wherein suppressing CSD prevents or treats a chronic headache selected from a group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, and an inflammatory headache. Support

for Claim 54 is found in the specification as filed at p. 10, line 32 and 11, lines 1 and 11-24.

New Claim 55 recites a method of treating a CSD-associated condition selected from the group consisting of a head injury, transient global amnesia, and intracranial hemorrhage, the method comprising administering to the subject an effective amount of (R)-2-acetamido-N-benzyl-3-methoxypropionamide. Support for Claim 55 is found in the specification as filed at p. 10, lines 11-12 and 24 and p. 11, lines 5-11.

No new matter is added and no change of inventorship is believed to result from the amendment of claims as proposed herein.

Applicant reserves the right to reintroduce any cancelled subject matter in one or more later-filed continuation applications.

RESPONSE TO OFFICE ACTION DATED 1 OCTOBER 2010

Elections/Restrictions

The Office Action states at pg. 2 that Applicant elected SPM-927 without traverse in the Reply filed on 4 Dec 2009. This is incorrect. Applicant's Reply dated 4 Dec 2009 elected SPM-927 as a species of Formula IIb with traverse. Reasons for the traversal were outlined on pg. 13 of the 4 Dec 2009 Response as well.

1. Rejection Under 35 U.S.C. §102(b) and §102(e)

Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, and 46-47 stand rejected under 35 U.S.C. §102(b) over US Patent Application No. 2002/0086828 Harris (herein "Harris '828") and under §102(e) over US Patent 6,884,910 (herein "Harris '910"). These rejections are respectfully traversed.

1.1. Claim 1: A Method of Treating A Condition Associated With CSD

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. The Office Action agrees that this is not the case "with respect to the methods of treatment of a condition associated with cortical spreading depression." *See* Office Action, at p. 12. Therefore, Claim 1 as amended herein is novel over Harris '828 and Harris '910. However, Applicant notes for the record that a method of preventing a condition associated with cortical spreading depression (CSD) is novel over the cited art since neither Harris '828 nor '910 expressly or inherently

discloses CSD.

Claims 14, 16-18, 20, 24, and 32-36 each depend directly or indirectly from Claim 1, and are, thus, novel for at least the same reasons that Claim 1 is novel. Claims 2-4 and 41 are cancelled by present amendment, and thus, such rejection is moot.

1.2. Claim 44: A Method of Suppressing CSD

Both Harris '828 and '910 fail to expressly or inherently disclose CSD, much less a method of suppressing CSD as recited in Claim 44. However, Claim 44 is cancelled by present amendment, and thus, such rejection to Claim 44 is moot.

1.3. Claims 46 and 47: A Method of Suppressing CSD to Prevent or Treat a *Markush* Group of Headaches

Although Claim 46 is rejected, the 39-page Office Action fails to address the fact that neither Harris '828 nor Harris '910 recites a headache selected from the group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, or an inflammatory headache. Since Harris '828 and Harris '910 fail to expressly or inherently disclose any of the *Markush* group of headaches, Claim 46 is novel over Harris '828 and Claim 46 is novel over Harris '910 for at least this reason. Furthermore, Harris '828 and Harris '910 also fail to expressly or inherently disclose CSD, much less a method of suppressing CSD.

Claim 47 depends directly from Claim 46, and is, thus, novel for at least the same reasons that Claim 46 is novel.

Withdrawal of the present rejection under 35 U.S.C. §102(b) and 35 U.S.C. §102(e) is respectfully requested.

2. Rejection Under 35 U.S.C. §103(a) Over Harris '828 and Harris '910

Claims 1, 26-31, 42-45, and 52 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein "Harris '828") and over US Patent 6,884,910 (herein "Harris '910"). This rejection is respectfully traversed.

For ease of review and because Harris '828 and the Harris '910 patent contain parallel disclosure, all arguments presented below refer and cite to Harris '828.

2.1 Claim 1: A Method of Treating A Condition Associated With CSD

The Office Action (p. 21) states that “Applicant’s arguments have been carefully considered and are deemed persuasive with respect to the methods of treatment of a condition associated with cortical spreading depression.” Therefore, Claim 1, as amended herein, is non-obvious over Harris ‘828.

Claims 26-31 and 42-43 each depend directly or indirectly from Claim 1, and, thus, the Office Action fails to establish a presumption of *prima facie* obviousness for at least the same reasons that make amended Claim 1 non-obvious.

2.2. Claim 52: A Method of Suppressing CSD

The 39-page Office Action provides no rationale why Claim 52, directed to a method of suppressing CSD, is obvious over the cited art. For this reason alone, the Office Action fails to establish a presumption of *prima facie* obviousness.

The Office Action (p. 22), however, does state that Harris ‘828 reports dosages analogous to the Applicant’s specification and

[t]herefore, the limitation drawn to ‘amount effective to suppress CSD’ is met by the references...and thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Even if the dosage of treating a migraine as reported by Harris ‘828 and suppressing CSD as disclosed by Applicant are the same (which is not admitted herein):

- (a) Harris ‘828 fails to expressly or inherently disclose CSD; or
- (b) Provide any teaching/examples of what would be required to suppress CSD, much less that the dosage would be similar;

Accordingly, there is no motivation in Harris ‘828 to treat CSD, much less how to effectively suppress CSD.

Furthermore, the 39-page Office Action fails to address the evidence of unpredictability set forth in Applicant’s 9 July 2010 Response. The Office has not responded to Applicant’s argument per MPEP 707.07(f) which requires Examiners to answer all material traversed. Therefore, for the Office’s convenience, Applicant repeats its evidence of unpredictability: “The underlying mechanism and physiological role of these blood flow related changes observed in CSD are still not fully understood.” *See* application as filed, at p. 8, lines 9-11.

Iadecola also questions “what triggers CSD” and suggests that, at times, “the mechanisms triggering CSD remain obscure.” Iadecola (Feb. 2002) Nature Medicine 8(2):110-112, at p. 111, col. 3; *see also* Ebersberger, at p. 11, col. 2 (“collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches”). If the triggering mechanisms are obscure and CSD is not fully understood itself, how could the ordinary artisan predict that SPM-927 would work to suppress CSD? Rather, the evidence of a lack of understanding CSD, suggests that the “likely” outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for non-obviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for non-obviousness stronger.)

In this unpredictable and complex art, Applicant was the first to identify SPM-927 as a compound that could suppress CSD. Accordingly, even if known to effectively reduce pain in migraine headaches generally, it could not have been predicted that SPM-927 could suppress CSD.

Therefore, for at least these reasons a presumption of *prima facie* obviousness has not been established for Claim 52 over Harris ‘828 or Harris ‘910.

By present amendment, Claims 44 and 45 are cancelled and thus, such rejection to Claims 44 and 45 is moot.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

3. Rejection Under 35 U.S.C. §103(a) Over Harris ‘828 and Harris ‘910

Claims 40 and 44-49 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein “Harris ‘828”) and over US Patent 6,884,910 (herein “Harris ‘910”). This rejection is respectfully traversed.

3.1 Claim 40: A Method of Treating A Condition Associated With CSD

Claim 40, depends from Claim 1 which was rejected in the first 35 U.S.C. §103(a) over Harris ‘828 and Harris ‘910. Accordingly, Applicant references Sec. 2.1 above which more fully articulates the reasons why a presumption of *prima facie* obviousness has not been established for Claim 1, and thus, dependent Claim 40, over Harris ‘828 or Harris ‘910.

3.2 Claims 44 and 45: A Method of Suppressing CSD

By present amendment, Claims 44 and 45 are cancelled and thus, such rejection to Claims 44 and 45 is moot.

3.3. Claim 46: A Method of Suppressing CSD to Prevent or Treat a *Markush* Group of Headaches

Independent Claim 46 is rejected for the first time in this second rejection over 35 U.S.C. §103(a) over Harris '828 or Harris '910. Again, the Office Action provides no discussion of why Claim 46 is *prima facie* obvious in view of Harris '828 or Harris '910 – as the “response to arguments” is the same in both of the 35 U.S.C. §103(a) rejections over Harris '828 or Harris '910. Independent Claim 46 is directed to a method of suppressing CSD to prevent or treat a headache selected from the recited *Markush* group by administering an oral effective amount of SPM-927. Harris '828 and Harris '910 do not teach or suggest any of the types of headaches recited in Claim 46's *Markush* group. Moreover, there is no disclosure of a method of suppressing CSD. *See* Secs 1.3 and 2.2. Therefore, a presumption of *prima facie* obviousness has not been established for Claim 46, and thus, dependent Claims 47-49, over Harris '828 or Harris '910.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

4. Rejection Under 35 U.S.C. §103(a) Over Harris '828 or Harris '910 In View of Iadecola

Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, and 46-47 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein “Harris '828”) in view of Iadecola (Feb. 2002) Nature Medicine 8(2):110-112 (herein “Iadecola”) and over US Patent 6,884,910 (herein “Harris '910”) in view of Iadecola. These rejections are respectfully traversed.

4.1 Claim 1: A Method of Treating A Condition Associated With CSD

The Office Action (p. 21) states that “Applicant's arguments have been carefully considered and are deemed persuasive with respect to the methods of treatment of a condition associated with cortical spreading depression.” Therefore, Claim 1, as amended herein, is non-obvious over Harris '828 and Harris '910.

Moreover, the Office Action is focused on migraines and amended Claim 1 recites the CSD-associated-condition is a chronic headache selected from a group consisting of a muscle

contraction headache, a toxic headache, a cluster headache, a traction headache, and an inflammatory headache. Neither Harris '828 nor Harris '910 nor Iadecola teach or suggest any of the types of headaches recited in Claim 1.

Although migraine disclosure is not relevant in light of amended Claim 1, Applicant addresses the statement in the Office Action at p. 31:

[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of treating migraines of Harris in the 15-20% of migraine sufferers that had auras due to CSD as taught by Iadecola or having acute migraines.

First, neither the statement above nor anywhere else in the Office Action provides any rationale why it would have been obvious to treat migraines associated with CSD from the cited art. Second, even the Office agrees that neither Harris '828 nor '910, teaches or suggests a method of treating conditions associated with CSD (Office Action, pg. 12 and 26). Iadecola further strengthens Applicant's argument that there is no motivation from Harris '828 or Harris '910 to treat a condition associated with CSD with SPM-927. Iadecola concludes by addressing three major issues that remain unresolved:

- (1) "what triggers CSD?"
- (2) "whether the aura is an absolute requirement for the headache"; and
- (3) "how accurately does a rodent model mimic the human disease, and can this model be used to develop new therapies."

See also Ebersberger, *et al.* (2001) Ann Neurol, 49:7-13, p. 11, col. 2 ("collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches"). Accordingly, because Harris '828 fails to teach or suggest SPM-927 for treating a condition associated with CSD, and because Iadecola and Ebersberger, *et al.* question the relationship between CSD and migraines, neither Harris '828 nor Iadecola provide any motivation to one of ordinary skill to treat a condition associated with CSD with SPM-927, much less a CSD-associated-condition selected from the *Markush* group of Claim 1.

Furthermore, the Office Action (p. 32) states:

[o]ne of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Harris *et al.* are

drawn to preventing and treating any migraine, including those associated with CSD and/or acute migraines since Harris is not limited to preventing/treating a certain the type [*sic*] of migraines.

However, as stated above, “[t]he underlying mechanism and physiological role of these blood flow related changes observed in CSD are still not fully understood.” *See* application as filed, at p. 8, lines 9-11. Iadecola questions “what triggers CSD” and suggests that, at times, “the mechanisms triggering CSD remain obscure.” Iadecola, at p. 111, col. 3; *see also* Ebersberger, at p. 11, col. 2. If the triggering mechanisms are obscure and CSD is not fully understood itself, how could the ordinary artisan predict that SPM 927 would work to treat or prevent a condition associated with CSD, much less the CSD-associated-conditions recited in Claim 1? Rather, the evidence of a lack of understanding CSD, suggests that the “likely” outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for non-obviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for non-obviousness stronger.)

Claims 14, 16-18, 20, 24, and 32-36 directly or ultimately depend from Claim 1, and are thus non-obvious at least for all of the aforementioned reasons that make Claim 1 non-obvious. Claims 2-4 and 41 are cancelled and thus, such rejection is moot.

4.2 Claim 44: A Method of Suppressing CSD

Again, the Office Action rejects Claim 44 but fails to specifically address why a claim directed to a method of suppressing CSD is *prima facie* obvious over the cited art. However, Claim 44 is cancelled and thus, such rejection to Claim 44 is moot.

4.3 Claim 46: A Method of Suppressing CSD to Prevent or Treat a *Markush* Group of Headaches

Again, the Office Action provides no discussion of why Claim 46 is *prima facie* obvious in view of Harris '828 or Harris '910 in view of Iadecola. Independent Claim 46 is directed to a method of suppressing CSD to prevent or treat a headache selected from the recited *Markush* group by administering an oral effective amount of SPM-927. Neither Harris '828 nor Harris '910 nor Iadecola teach or suggest any of the types of headaches recited in Claim 46's *Markush* group.

Further, Harris '828 and Harris '910 do not even disclose CSD, therefore Harris '828 and Harris '910 can not teach or suggest a method for suppressing CSD. Harris deals with "treating pain, in particular neuropathic pain, bipolar disease and migraine headaches." See Harris '828, at abstract. While Harris '828 and '910 are directed to pain associated, in part, with migraine headaches, Applicant's Claim 46 is directed a method to suppress CSD. Therefore, a presumption of *prima facie* obviousness has not been established for Claim 46 over Harris '828 in view of Iadecola or Harris '910 in view of Iadecola.

Claim 47 depends from Claim 46, and is thus non-obvious at least for all of the aforementioned reasons that make Claim 46 non-obvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

5. Rejection Under 35 U.S.C. §103(a) Over Harris '828 or Harris '910 In View of Iadecola

Claims 1, 26-31, 42-45, and 52 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein "Harris '828") in view of Iadecola (Feb. 2002) *Nature Medicine* 8(2):110-112 (herein "Iadecola") and over US Patent 6,884,910 (herein "Harris '910") in view of Iadecola. These rejections are respectfully traversed.

In making this second 35 U.S.C. §103 rejection over Harris '828 in view of Iadecola or Harris '910 in view of Iadecola, the Examiner's discussion is limited to the recited dosages and mode of administration in the dependent claims. None of the Examiner's discussion addresses the elements of the independent claims, for example that (1) neither Harris '828, Harris '910, nor Iadecola teaches or suggests a method for treating a condition associated with CSD (Claim 1) and (2) neither Harris '828, Harris '910, nor Iadecola teaches or suggests a

method for suppressing CSD (Claim 52). Therefore, a presumption of *prima facie* obviousness has not been established.

5.1 Claim 1: A Method of Treating A Condition Associated With CSD

At the outset, Applicant is uncertain why Claim 1 is rejected twice with the same references. Accordingly, Applicant references Sec. 4.1 above which more fully articulates the reasons why a presumption of *prima facie* obviousness has not been established for Claim 1 over Harris '828 in view of Iadecola or Harris '910 in view of Iadecola, and thus, dependent Claims 26-31 and 42-43.

5.2 Claim 52: A Method of Suppressing CSD

Claim 52 recites a method of suppressing CSD. Applicant incorporates its response in Sec. 4.3. As set forth above, Harris '828 and Harris '910 fail to disclose the element CSD, much less teach or suggest a method for suppressing CSD, much less the effective dosage for suppressing CSD. Iadecola also fails teach or suggest a method for suppressing CSD, much less the effective dosage for suppressing CSD. Therefore, for at least these reasons a presumption of *prima facie* obviousness has not been established for Claim 52 over Harris '828 in view of Iadecola or Harris '910 in view of Iadecola.

Claims 44 and 45 are cancelled, and thus, such rejection to Claims 44 and 45 is moot.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

6. Rejection Under 35 U.S.C. §103(a) Over Harris '828 and Harris '910 In View of Iadecola

Claims 40 and 44-49 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein "Harris '828") in view of Iadecola (Feb. 2002) Nature Medicine 8(2):110-112 (herein "Iadecola") and over US Patent 6,884,910 (herein "Harris '910") in view of Iadecola. These rejections are respectfully traversed.

6.1 Claim 40: A Method of Treating A Condition Associated With CSD

Claim 40, depends from Claim 1, which was rejected in the first and second 35 U.S.C. §103(a) over Harris '828 in view of Iadecola and Harris '910 in view of Iadecola. Accordingly, Applicant references Secs. 4.1 and 5.1 above which more fully articulates the reasons why a presumption of *prima facie* obviousness has not been established for Claim 1, and thus, dependent Claim 40.

6.2 Claim 46: A Method of Suppressing CSD to Prevent or Treat a *Markush* Group of Headaches

Although Claim 46 is rejected, the 39-page Office Action fails to address the fact that neither Harris '828, nor Harris '910, nor Iadecola recites a headache selected from the group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, or an inflammatory headache. Since each of Harris '828 and Harris '910 fail to expressly or inherently disclose any of the *Markush* group of headaches, a presumption of *prima facie* obviousness has not been established for Claim 46.

Furthermore, Claim 46 recites a method of suppressing CSD. Applicant incorporates its response in Secs. 4.3 and 5.2. As set forth above, Harris '828 and Harris '910 fail to disclose the element CSD, much less teach or suggest a method for suppressing CSD. Iadecola also fails teach or suggest a method for suppressing CSD. Therefore, for at least these reasons a presumption of *prima facie* obviousness has not been established for Claim 46 over Harris '828 in view of Iadecola or Harris '910 in view of Iadecola.

Claims 47-49 depend directly from Claim 46, and are, thus, non-obvious for at least the same reasons that Claim 46 is non-obvious. Claims 44 and 45 are cancelled, and thus, such rejection to Claims 44 and 45 is moot.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

7. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Office Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

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Respectfully submitted,

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